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Practitioner's Docket No. U 012500-4

CHAPTER II

TRANSMITTAL LETTER TO THE UNITED STATES ELECTED OFFICE (EO/US)

(ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

PCT/ES98/00145	25 MAY 1998	29 MAY 1997
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED

PROCESS FOR OBTAINING QUINAPRYL HYDROCHLORIDE AND SOLVATES USEFUL FOR ISOLATING AND PURIFYING QUINAPRYL HYDROCHLORIDE
TITLE OF INVENTION

Montserrat **MONSALVATJE LLAGOSTERA**; Marti **BARTRA SANMARTI**; Jaime **TOMAS NAVARRO**; Salvador **PUIG TORRES**
APPLICANT(S)

Box PCT
Assistant Commissioner for Patents
Washington D.C. 20231
ATTENTION: EO/US

NOTE The completion of those filing requirements that can be made at a time later than 30 months from the priority date results from the Commissioner exercising his judgment under the authority granted under 35 USC 371(d). The filing receipt will show the actual date of receipt of the last item completing the entry into the national phase See 37 C F R §1.491 which states "An international application enters the national state when the applicant has filed the documents and fees required by 35 USC 371(c) within the periods set forth in § 1 494 and § 1 495."

CERTIFICATION UNDER 37 C.F.R. 1.10*
*(Express Mail label number is **mandatory**.)*
(Express Mail certification is optional.)

I hereby certify that this correspondence and the documents referred to as attached therein are being deposited with the United States Postal Service on this date NOVEMBER 29, 1999, in an envelope as "Express Mail Post Office to Addressee," Mailing Label Number EL386266139US, addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

CONNIE YANNOTTI
(type or print name of person mailing paper)

Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C F.R. 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence*

***WARNING:** *Each paper or fee filed by "Express Mail" **must** have the number of the "Express Mail" mailing label placed thereon prior to mailing 37 C.F.R. 1 10(b)*
*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

EL386266139US

WARNING: *Where the items are those which can be submitted to complete the entry of the international application into the national phase are subsequent to 30 months from the priority date the application is still considered to be in the international state and if mailing procedures are utilized to obtain a date the express mail procedure of 37 C.F.R. §1.10 must be used (since international application papers are not covered by an ordinary certificate of mailing - See 37 C F.R. §1.8.*

NOTE *Documents and fees must be clearly identified as a submission to enter the national state under 35 USC 371 otherwise the submission will be considered as being made under 35 USC 111. 37 C.F.R. § 1.494(f).*

1. Applicant herewith submits to the United States Elected Office (EO/US) the following items under 35 U.S.C. 371:

   a. [x] This express request to immediately begin national examination procedures (35 U.S.C. 371(f)).

   b. [x] The U.S. National Fee (35 U.S.C. 371(c)(1)) and other fees (37 C.F.R. § 1.492) as indicated below:

2.Fees

CLAIMS FEE	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
[ ]*	TOTAL CLAIMS	14 - 20 =		x $ 18.00 =	$
	INDEPENDENT CLAIMS	1 - 3 =		x $ 78.00 =	
	MULTIPLE DEPENDENT CLAIM(S) (if applicable) + $260.00				
BASIC FEE**	[ ] U.S. PTO WAS INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where an International preliminary examination fee as set forth in § 1.482 has been paid on the international application to the U.S. PTO: [ ] and the international preliminary examination report states that the criteria of novelty, inventive step (non-obviousness) and industrial activity, as defined in PCT Article 33(2) to (4) have been satisfied for all the claims presented in the application entering the national stage (37 CFR 1.492(a)(4)) ..... $96.00 [ ] and the above requirements are not met (37 CFR 1.492(a)(1)) ..... $670.00 [X] U.S. PTO WAS NOT INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where no international preliminary examination fee as set forth in § 1.482 has been paid to the U.S. PTO, and payment of an international search fee as set forth in § 1.445(a)(2) to the U.S. PTO: [ ] has been paid (37 CFR 1.492(a)(2)) ..... $760.00 [ ] has not been paid (37 CFR 1.492(a)(3)) ..... $970.00 [X] where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 CFR 1.492(a)(5)) $840.00				$840.00
	Total of above Calculations				=$840.00
SMALL ENTITY	Reduction by ½ for filing by small entity, if applicable. Affidavit must be filed. (note 37 CFR 1.9, 1.27, 1.28)				-
	Subtotal				
	Total National Fee				$
	Fee for recording the enclosed assignment document $40.00 (37 CFR 1.21(h)). (See Item 13 below). See attached "ASSIGNMENT COVER SHEET".				
TOTAL	Total Fees enclosed				$840.00

*See attached Preliminary Amendment Reducing the Number of Claims.

i. [X] A check in the amount of $840.00 to cover the above fees is enclosed.

ii. [ ] Please charge Account No. _____ in the amount of $ _____.
A duplicate copy of this sheet is enclosed.

**WARNING. *"To avoid abandonment of the application the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 30 months from the priority date: * * * (2) the basic national fee (see § 1 492(a)). The 30-month time limit may not be extended." 37 C.F.R. § 1.495(b)*

WARNING: *If the translation of the international application and/or the oath or declaration have not been submitted by the applicant within thirty (30) months from the priority date, such requirements may be met within a time period set by the Office. 37 C.F R § 1.495(b)(2). The payment of the surcharge set forth in § 1.492(e) is required as a condition for accepting the oath or declaration later than thirty (30) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than thirty (30) months after the priority date. Failure to comply with these requirements will result in abandonment of the application The provisions of § 1.136 apply to the period which is set. Notice of Jan. 3, 1993, 1147 O.G. 29 to 40.*

3. [X] A copy of the International application as filed (35 U.S.C. 371(c)(2)):

NOTE *Section 1.495 (b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 30 months from the priority date to avoid abandonment "The International Bureau normally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies applicant of the communication to the Office In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage, the applicant normally need only check to be sure the notice from the International Bureau has been received and then pay the basic national fee by 30 months from the priority date." Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35-36. See item 14c below.*

a. [ ] is transmitted herewith.

b. [ ] is not required, as the application was filed with the United States Receiving Office.

c. [X] has been transmitted

i. [ ] by the International Bureau.
Date of mailing of the application (from form PCT/IB/308): _____.

ii. [X] by applicant on MAY 25, 1998.
Date

4. [X] A translation of the International application into the English language (35 U.S.C. 371(c)(2)):

a. [X] is transmitted herewith.

b. [ ] is not required as the application was filed in English.

c. [ ] was previously transmitted by applicant on _____.
Date

d. [ ] will follow.

5. [X] Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. 371(c)(3)):

NOTE The Notice of January 7, 1993 points out that 37 C.F.R. § 1.495(a) was amended to clarify the existing and continuing practice that PCT Article 19 amendments must be submitted by 30 months from the priority date and this deadline may not be extended The Notice further advises that: "The failure to do so will not result in loss of the subject matter of the PCT Article 19 amendments. Applicant may submit that subject matter in a preliminary amendment filed under section 1.121. In many cases, filing an amendment under section 1.121 is preferable since grammatical or idiomatic errors may be corrected " 1147 O.G. 29-40, at 36.

a. [ ] are transmitted herewith.
b. [ ] have been transmitted
   i. [ ] by the International Bureau.
   Date of mailing of the amendment (from form PCT/IB/308): _____.
   ii. [ ] by applicant on _____.
   Date
c. [X] have not been transmitted as
   i. [X] applicant chose not to make amendments under PCT Article 19.
   Date of mailing of Search Report (from form PCT/ISA/210): SEPT. 21, 1998.
   ii. [ ] the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. [X] A translation of the amendments to the claims under PCT Article 19 (38 U.S.C. 371(c)(3)):
a. [ ] is transmitted herewith.
b. [ ] is not required as the amendments were made in the English language.
c. [X] has not been transmitted for reasons indicated at point 5(c) above.

7. [X] A copy of the international examination report (PCT/IPEA/409)
[X] is transmitted herewith.
[ ] is not required as the application was filed with the United States Receiving Office.

8. [X] Annex(es) to the international preliminary examination report
a. [X] is/are transmitted herewith.
b. [ ] is/are not required as the application was filed with the United States Receiving Office.

9. [X] A translation of the annexes to the international preliminary examination report
a. [ ] is transmitted herewith.
b. [X] is not required as the annexes are in the English language.

10. [X] An oath or declaration of the inventor (35 U.S.C. 371(c)(4)) complying with 35 U.S.C. 115
    a. [ ] was previously submitted by applicant on _____. Date
    b. [ ] is submitted herewith, and such oath or declaration
        i. [ ] is attached to the application.
        ii. [ ] identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or 3(c) and 5(b); and states that they were reviewed by the inventor as required by 37 C.F.R. 1.70.
    c. [X] will follow.

Other document(s) or information included:

11. [X] An International Search Report (PCT/ISA/210) or Declaration under PCT Article 17(2)(a):
    a. [X] is transmitted herewith.
    b. [ ] has been transmitted by the International Bureau.
    Date of mailing (from form PCT/IB/308): _____.
    c. [ ] is not required, as the application was searched by the United States International Searching Authority.
    d. [ ] will be transmitted promptly upon request.
    e. [ ] has been submitted by applicant on _____. Date

12. [X] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98:
    a. [X] is transmitted herewith.
    Also transmitted herewith is/are:
    [X] Form PTO-1449 (PTO/SB/08A and 08B).
    [X] Copies of citations listed.
    b. [ ] will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. 371(c).
    c. [ ] was previously submitted by applicant on _____. Date

13. [ ] An assignment document is transmitted herewith for recording.

A separate [ ] "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or [ ] FORM PTO 1595 is also attached.

_____
_____
_____

14. [X] Additional documents:
    a. [ ] Copy of request (PCT/RO/101)
    b. [X] International Publication No. WO 98/54149
        i. [ ] Specification, claims and drawing
        ii. [X] Front page only
    c. [ ] Preliminary amendment (37 C.F.R. § 1.121)
    d. [X] Other

    Response to Written Opinion

15. [X] The above checked items are being transmitted .
    a. [X] before 30 months from any claimed priority date.
    b. [ ] after 30 months.

16. [ ] Certain requirements under 35 U.S.C. 371 were previously submitted by the applicant on _____, namely:

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges if extra claims are authorized.*

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1 17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R § 1.136(a)(3).

NOTE. "Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C F.R § 1 26(a)

[X] The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. 12-0425.

[X] 37 C.F.R. 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 30 months without extension (37 C.F.R § 1 495(b)(2)) results in abandonment of the application, it would be best to always check the above box.*

[ ] 37 C.F.R. 1.492(b), (c) and (d) (presentation of extra claims)

NOTE Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must

only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.492(d)), it might be best not to authorize the PTO to charge additional claim fees, except possible when dealing with amendments after final action

[X] 37 C.F.R. 1.17 (application processing fees)
[X] 37 C.F.R. 1.17(a)(1)-(5)(extension fees pursuant to § 1.136(a).
[X] 37 C.F.R. 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. 1.311(b))

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance 37 C F R. § 1.311(b).

NOTE. 37 C.F.R. 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . prior to paying, or at the time of paying . . issue fee." From the wording of 37 C.F R. § 1 28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

[X] 37 C.F.R. § 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 30 months after the priority date).

SIGNATURE OF PRACTITIONER

Reg. No.: 25, 858

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(type or print name of practitioner)
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PROCESS FOR OBTAINING QUINAPRIL HYDROCHLORIDE AND SOLVATES USEFUL FOR THE ISOLATION AND PURIFICATION OF QUINAPRIL HYDROCHLORIDE

FIELD OF THE INVENTION

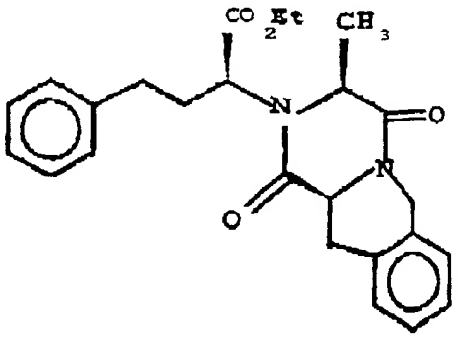
This invention refers to a procedure for obtaining quinapril hydrochloride, as well as new solvates of quinapril hydrochloride, obtained by the use of Class 3 solvents, from which it is possible to eliminate the solvent by drying without degradation of the product, and which are useful for the isolation and purification of quinapril hydrochloride. The process can be developed at the industrial scale.

BACKGROUND OF THE INVENTION

Quinapril is the common international denomination of the chemical compound named (S)-2- [(S)-N- [(S) -1-(ethoxycarbonyl- 3-phenylpropyl] -L-alanyl] -1,2,3,4-tetrahydro-3- isoquinolinecarboxylic acid]. Quinapril and its pharmaceutically acceptable salts are antihypertensive agents which act as angiotensin converting enzyme (ACE) inhibitors.

The first description of quinapril appears in the United States Patent No. US 4.344.949, which also describes its preparation starting from the ethyl ester of (S,S)- α-[(1- carboxyethyl) amino] phenylbutanoic acid and from the benzyl or t-butyl ester of (S)-1,2,3,4- tetrahydro -3-isoquinolinecarboxylic acid by peptide condensation with dicyclohexyl- carboimide (DCC) and activation with hydroxibenzotriazole. The benzyl or t-butyl ester of quinapril so obtained is unprotected by catalytic hydrogenation or by treatment with trifluoroacetic acid, being the final isolation of quinapril carried out (at the

laboratory scale) by precipitation with ethyl ether and by lyophilization of an aqueous solution. The isolation of quinapril is a very delicate procedure, as this product degrades very easily by intramolecular cyclisation to yield a diketopiperazine of formula



both in aqueous or organic solution as in the solid state.

The process described in said patent US 4.344.949 presents the drawbacks which are typical of the use of DCC, as the condensations carried out in the presence of DCC yield a fair amount of impurities, with the subsequent reduction in the yield (61%), thus the resulting dicylohexylurea must be separated and, additionally, the carbodiimides are responsible for very severe allergies.

Quinapril hydrochloride is the salt which is usually employed in the manufacture medicinal products which contain quinapril.

The United States Patent No. 4.761.479 mentions that obtaining and purifying quinapril hydrochloride is hindered by its ease in degrading into by-products, essentially the diketopiperazine shown before. Said US patent No. 4.761.479 describes a process for obtaining quinapril hydrochloride which comprises unprotecting the t-butyl ester of quinapril with HCl gas in acetic acid, the isolation of the precipitation product after the addition of xylene and vacuum distillation, and the purification of the quinapril

hydrochloride by crystallisation with acetonitrile to yield a crystalline solvate of acetonitrile. The solvent of said solvate can be removed, without degradation of the quinapril hydrochloride, by drying in a vacuum oven. However, acetonitrile is a Class 2 solvent, defined by the ICH [International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use] as a "Non-mutagenic carcinogen in animals or possible cause of other irreversible toxicity such as neurotoxicity, teratogenesis or suspect of significant reversible toxicity, and, therefore, its proportion has to be limited". In the case of acetonitrile, the ICH recommends a limit not above 250 ppm (0.025%). This limit is difficult to achieve at the industrial scale due to the little stability of the product.

The Belgian Patent No. BE 892.552 describes another process for the preparation of quinapril hydrochloride starting from (S,S)- α- [(1- carboxyethyl) amino] phenylbutanoic acid by activation with 1,1' -carbonyldiimidazole, which yields an N-carboxyanhydride which reacts *in situ*, without prior isolation, with the benzyl ester of (S)-1,2,3,4- tetrahydro -3- isoquinolinecarboxylic acid to yield the corresponding benzyl ester of quinapril with a yield of 56%. The resulting quinapril, protected in the form of a benzyl ester, is subsequently hydrogenated in the presence of Pd/C and it is treated with hydrochloric acid to give the quinapril hydrochloride, which is purified by chromatography and lyophilization, at a very low yield (37%). This synthetic route is also mentioned in a generic manner in the Spanish Patent ES 2.004.804, but without giving any specific conditions, nor yields, nor a description of the properties of the products obtained. Specifically, the synthesis of quinapril hydrochloride is not exemplified at all.

In general, all the processes described for obtaining quinapril hydrochloride are characterised by their difficulty or by their low yields. Only the US Patent US 4.761.479 describes a process for the industrial isolation and purification of quinapril hydrochloride, starting from the t-butyl ester of quinapril. However, said procedure has the disadvantage of using a carcinogenic solvent (acetonitrile) to obtain the corresponding solvate.

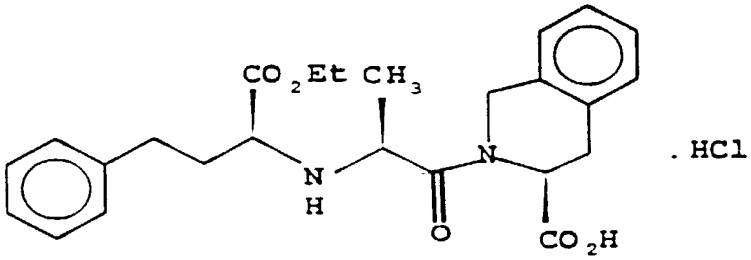
Consequently, there is a need to have a process for obtaining and purifying quinapril hydrochloride, which may be carried out at the industrial scale, and which overcomes the previously mentioned drawbacks. In order to obtain and purify quinapril hydrochloride at a high yield, the invention proposes the precipitation of said product in the form of a toluene solvate. Therefore, one of the objects of the invention is constituted by a process for obtaining quinapril hydrochloride, which comprises its isolation as the toluene solvate.

On the other hand, the solvates of quinapril hydrochloride, which are useful compounds for the purification of said product, are, in general, products from which it is extremely difficult to remove the solvent without partially degrading the quinapril hydrochloride. The only known solvate of quinapril hydrochloride which can be dried without degradation of the product is the acetonitrile solvate, but said solvate has been obtained with a carcinogenic solvent. In order to overcome these drawbacks, the invention provides solvates of quinapril hydrochloride which can be dried to remove the solvent without degrading the quinapril hydrochloride, and which have been obtained by the use of non-carcinogenic solvents. Therefore, an additional object of the invention is constituted by new solvates of quinapril hydrochloride, of solvents belonging to Class 3, from which it is possible to remove the solvent by drying without degradation of

quinapril hydrochloride. Class 3 solvents are defined, according to the ICH, as "Solvents with a low toxic potential to man, not being it necessary to establish an exposure limit based on health criteria. Class 3 solvents have a ADE (Allowable Daily Exposure) equal or greater than 50 mg per day".

DETAILED DESCRIPTION OF THE INVENTION

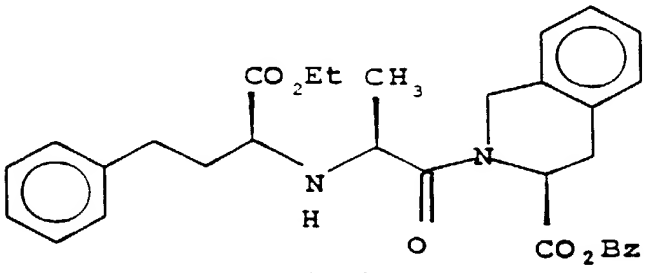
The invention provides a process for obtaining quinapril hydrochloride of formula (I)



(I)

which comprises the stages of:

a) hydrogenolysis of the benzyl ester of quinapril (II)



(II)

where Bz is the benzyl radical;

b) removal of the solvent used in step a);

c) addition of toluene to precipitate the quinapril hydrochloride as a toluene solvate;

d) treatment of the toluene solvate of quinapril hydrochloride with a solvent belonging to Class 3, capable of forming a solvate of quinapril hydrochloride from which it is possible to eliminate said solvent by drying in an oven without degrading the quinapril hydrochloride; and
e) drying of the solvate obtained in step d) to yield quinapril hydrochloride (I).

The benzyl ester of quinapril (II) is a known product which can be obtained by whichever of the processes described in the patents US 4.344.949 and BE 892.552, mentioned earlier, as well as in the patents EP 135181 and EP 135182 where it is described, in a general manner, the obtaining of the protected quinapril in the form of the benzyl ester starting from (S,S)- α- [(1- carboxyethyl) amino] phenylbutanoic acid, by activation with alkenephosphonic anhydrides.

The hydrogenolysis of the benzyl ester of quinapril (II) can be carried out in an alcoholic solvent, such as ethanol or isopropanol, with concentrated hydrochloric acid or with a solution of hydrogen chloride in isopropanol, hydrogenation with hydrogen gas at a pressure comprised between approximately 10^4 Pa (0,1 bar) and approximately 2 x 10^5 Pa (2 bar), at a temperature comprised between 10 and 40 °C, in the presence of a suitable hydrogenation catalyst, for instance, Pd/C.

In a specific embodiment, the hydrogenolysis reaction is carried out using ethanol as a solvent, concentrated hydrochloric acid, a pressure of 10^5 Pa (1 bar) and room temperature. In another specific embodiment, the hydrogenolysis reaction is carried out using isopropanol as a solvent, a solution of hydrogen chloride in isopropanol, a pressure of 2 x 10^5 Pa (2 bar) and a temperature of approximately 30 °C.

The molar ratio between the benzyl ester of quinapril

(II) and hydrochloric acid can be equal or slightly greater to the stoichiometric one, although preferably said molar ratio is stoichiometric as, in the event of a large defect of hydrochloric acid, quinapril tends to cyclise to form the diketopiperazine shown above, while in the event of an excess of acid, decomposition of the quinapril hydrochloride, and of the benzyl ester of quinapril itself, takes place.

Generally, hydrochloric acid is added at room temperature, and the reaction between the hydrochloric acid and the benzyl ester of quinapril (II) is virtually immediate, within minutes.

Because the solution of the benzyl ester of quinapril hydrochloride in isopropanol is more stable than the solution of the free base and, on the other hand, considering the instability of the benzyl ester of quinapril (II), the most reliable manner of preserving such product for short periods of time is maintaining it as the hydrochloride in solution in isopropanol.

Once hydrogenation is finalised, the catalyst is removed, for example, by filtration, and the solvent employed, ethanol or isopropanol, is removed, for instance, by vacuum distillation, at a temperature below 40 °C, as at greater temperatures cyclisation of the product to form the diketopiperazine is quantitatively more significant, and toluene is added. These operations involving the removal of the solvent and addition of toluene can be repeated a variable number of times. Subsequently, the bulk of the reaction is allowed to stand at room temperature for the quinapril hydrochloride to precipitate in the form of the toluene solvate.

In a specific embodiment, for the obtaining of the toluene solvate of quinapril hydrochloride starting from the raw solution in the solvent used (ethanol or isopropanol), said solution is distilled down to a defined

volume of approximately 1,6 ml/g of benzyl ester of quinapril and subsequently, an amount of toluene of approximately 2,25 ml of toluene per gram of benzyl ester of quinapril is added. After this, distillation is carried out again to the same volume as before, and the same amount of toluene is added. By working under these conditions, quinapril hydrochloride precipitates in the form of the toluene solvate within a period of time comprised between 20 and 60 minutes. By following this precipitation process for the toluene solvate, using isopropanol as a solvent, a greater yield is obtained than by employing ethanol, which can largely be accounted for by the fact that quinapril hydrochloride is more soluble in ethanol than in isopropanol.

The toluene solvate of precipitated quinapril hydrochloride is filtered and dried, and a yield comprised between approximately 85% and 90% is obtained. This solvate is a very suitable intermediate for the subsequent purification of quinapril hydrochloride according to the process proposed by the present invention. The spectroscopic characteristics (IR, ^{1}H-NMR and ^{13}C-NMR) of this toluene solvate are contained in Example 2.1. The attempts made to remove the toluene by drying of said solvate, without degrading the quinapril hydrochloride, were unsuccessful.

Subsequently, the toluene solvate of quinapril hydrochloride is treated with a solvent belonging to Class 3, i.e., non-toxic, non-carcinogenic, for example, ethyl formate or methyl acetate, at a temperature comprised between 40 °C and 45 °C, for a period of time comprised between 1 and 2 hours, and it is next cooled down to a temperature comprised between 20 °C and 25 °C, for a period of time comprised between 1 and 2 hours, to form the corresponding solvate, either of ethyl formate or of methyl acetate, which is then filtered and dried, with a yield in

any of the cases of approximately 95%. These solvates can be dried in an oven, to remove the solvent, without degrading the quinapril hydrochloride. These solvates are key intermediates for obtaining quinapril hydrochloride of a high degree of purity (99.8%) according to the process object of this invention. The spectroscopic (IR, ^{1}H-NMR and ^{13}C-NMR) and X-Ray diffraction characteristics of these solvates are contained in Examples 2.2. and 2.3.

The drying of the ethyl formate or of the methyl acetate solvates of quinapril hydrochloride obtained in this manner, in order to yield quinapril hydrochloride, can be carried out in an oven, for example in a vacuum oven, at a temperature comprised between approximately 40 and 50 °C, for a period of time comprised between 12 and 24 hours, depending on the amount of solvate to be dried. The resulting quinapril hydrochloride, the spectroscopic (IR, ^{1}H-NMR and ^{13}C-NMR), optical rotation and X-Ray diffraction characteristics of which are collected in example 2.4., is an amorphous product, the X-ray diffraction patter of which exhibits few peaks and with a low intensity, and consequently, *a priori*, it is an amorphous product.

The hydrogenation of the product resulting after the addition of hydrochloric acid or of the solution of hydrogen chloride in isopropanol in step a) can be carried out without prior isolation of the intermediate formed. Equally, the bulk of the reaction resulting from the hydrogenolysis can be subjected to distillation in order to remove the solvent used in step a), without isolation of the product formed.

In a specific and preferred embodiment of the invention, the benzyl ester of quinapril is obtained by condensation of the N-carboxyanhydride of N-[1-(S)-ethoxycarbonyl -3-phenylpropyl]- L-alanine and of the benzyl ester of (S)-1,2,3,4- tetrahydro -3-isoquinolinecarboxylic acid. The resulting benzyl ester of

quinapril (II), without isolating, is subjected to the previously described treatment, for example, in patent BE 892.552.

The following examples serve the purpose of illustrating specific forms of embodiment of the process object of the invention, and they must not be considered as limiting to the scope of the same. All the X-ray diffraction analyses were carried out by the crystalline powder method (λ = 1,5419 Å), the preparations of the sample were performed on a dry standard.

Material of the anode: copper
Wavelength, λ_1 (Å) = 1,54060
Wavelength, λ_2 (Å) = 1,54439
Initial angle ($2\theta°$) : 6,025
Final angle ($2\theta°$) : 39,9855
Initial d value (Å) = 14,65735
Final d value (Å) = 2,25302

EXAMPLE 1

Preparation of the benzyl ester of (S,S,S) 2-[2- [(1-(ethoxycarbonyl)- 3-phenylpropyl) amino] 1-oxopropyl] - 1,2,3,4- tetrahydro-3- isoquinolinecarboxylic acid [benzyl ester of quinapril (II)]

51.3 g (0.12 moles) of the para-toluenesulfonate of the benzyl ester of (S)-1,2,3,4- tetrahydro - isoquinoline-3- carboxylic acid are suspended in 150 ml of toluene. 200 ml of 10% sodium bicarbonate solution are added under stirring and the mixture is shaken until complete dissolution is achieved. The organic phase is allowed to decant and it is separated, and the same is again washed with 100 ml of 10% sodium bicarbonate solution, and it is subsequently dried with sodium sulphate and filtered. To

this toluene based solution, 36.0 g (0.12 moles) of the N-carboxyanhydride of N-[1-(S)-ethoxycarbonyl -3-phenylpropyl]- L-alanine, dissolved in 75 ml of toluene, are added, at room temperature, in 1 hour. Approximately 4 hours after the addition of said N-carboxyanhydride, the reaction is finished. The toluene phase is washed with a 5% sodium hydroxide solution, followed by water, and the solvent is vacuum-distilled until an oil is obtained, 62 g (Yield: 98%) which is the benzyl ester of quinapril.

After forming the maleate, it is characterised by:

- HPLC: the has a purity of 99.3%
- Titration: 100.2%
- $[\alpha]^R$ = -12.93° (2% methanol)

IR (KBr) (ν, cm^{-1}) : 3520, 3050, 2980, 1746, 1656, 1603, 1455, 1347, 1211, 1010, 751, 697.

In solution, this compound is a mixture of two rotamers. The distribution of the rotamers is observed, in some cases, in the proton and carbon 13 nuclear magnetic resonance (NMR) spectra.

^{1}H-NMR ($CDCl_3$, 300 MHz) (δ(ppm)): 10,40 (wide band, 3H); 7,40-7,00 (m, 14 H); 6,29 (s, 2H); 5,43 (dd, J_1 = 3,9 Hz, J_2 = 5,9 Hz, 1H); 5,02 (m, 2H); 4,60 (m, 2H); 4,44 (q, $J_1 = J_2 = J_3$ = 7,1 Hz, 1H); 4,23 (m, 2H); 3,77 (t_{min}), 3,72 (t, J_1 = 6,3 Hz, 1H); 3,45 - 3,05 (m, 2H); 2,85 - 2,65 (m, 2H); 2,30 - 2,15 (m, 2H); 1,6 (d_{min}, J_1 = 6,8 Hz), 1,45 (d, J_1 = 6,9 Hz), 3H; 1,28 (t, $J_1 = J_2$ = 7,2 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz) (δ(ppm)): 170,4 (min), 170,1, 169,7 (min), 169,2 (min), 169,1, 139,6 (min), 139,5, 135,3, 135,1 (min), 134,5, 131,8, 131,3 (min), 130,9 (min), 130,7, 128,6, 128,5, 128,4, 128,3, 128,1, 128,0, 127,9, 127,8, 127,7, 127,4, 127,3, 126,6, 126,5, 126,4, 126,1, 67,9 (min), 67,2, 62,6, 62,4 (min), 59,5 (min), 58,6, 54,7 (min), 54,5 (min), 53,5, 52,6, 45,2, 44,5 (min), 32,4 (min), 32,1, 31,3 (min), 31,2, 30,5, 16,8 (min), 15,6, 14.0 (min), 13,9.

EXAMPLE 2

Preparation of (S,S,S) 2-[2- [(1-(ethoxycarbonyl)- 3-phenylpropyl) amino] 1-oxopropyl] -1,2,3,4-tetrahydroisoquinoline -3-carboxylic acid hydrochloride [Quinapril hydrochloride (I)]

2.1. Toluene solvate of quinapril hydrochloride.

62.0 g of the benzyl ester of quinapril, obtained according to Example 1, are dissolved with 400 ml of ethanol and 10 ml of concentrated hydrochloric acid, 3.1 g of 5% Pd/C (paste) catalyst are added and the mixture is hydrogenated at room temperature and at a pressure 10^5 Pa (1 bar) for 3 hours. After hydrogenation has concluded, the catalyst is filtered, most part of the ethanol is vacuum-distilled and 150 ml of toluene are added. Subsequently, most of the solvent is vacuum-distilled again and another 150 ml of toluene are added. Subsequently it is allowed to stand at room temperature, which leads to the precipitation of a solid which is filtered and dried under a vacuum at 40 °C. 58,5 g were obtained (Yield: 88%) of a product which corresponds to the toluene solvate of quinapril hydrochloride.

IR (KBr) (ν, cm^{-1}) : 3520, 3026, 3003, 2928, 2802, 1755, 1742, 1711, 1646, 1558, 1538, 1495, 1455, 1203, 758, 737.

In solution, this compound is a mixture of two rotamers. The distribution of the rotamers is observed, in some cases, in the proton and carbon 13 nuclear magnetic resonance (NMR) spectra.

^{1}H-NMR ($CDCl_3$, 300 MHz) (δ(ppm)): 7,20 - 7,00 (m, 14 H); 5,15 (t wide), 4,97 ($width_{min}$), 1H; 4,82 - 4,45 (m, 3H); 4,35 - 4,05 (m, 2H), 3,90 (t wide, 1H); 3,42 - 3,05 (m, 2H), 2,90 - 2,62 (m, 2H), 2,42 - 2,20 (m, 2H), 2,38 (s, 3H), 1,68 (d, J_1 = 6,2 Hz); 1,60 (d_{min}, J_1 = 6,2 Hz), 3H; 1,28 (t_{min}, $J_1 = J_2$ = 4,0 Hz); 1,22 (t, $J_1 = J_2$ = 4.0 Hz),

3H.

^{13}C-NMR ($CDCl_3$, 75 MHz) (δ(ppm)): 172,2, 171,4 (min), 169,2, 168,6, 168,2 (min), 168,0, 139,6 (min), 139,4, 137,8, 132,2, 131,4, 131,3, 131,2, 129,0, 128,6, 128,4, 128,2, 127,7, 127,1, 126,4, 126,3, 126,2, 125,2, 63,2 (min), 62,9, 59,1 (min), 58,9, 54,9 (min), 54,6 (min), 54,5, 53,1, 45,4, 44,1 (min), 31,9 (min), 31,4, 31,1, 31,0, 30,1 (min), 21,4, 16,2 (min), 15,2, 14,0 (min), 13,9.

2.2. Ethyl formate solvate of quinapril hydrochloride.

The 58.5 g of toluene solvate are shaken at 40 - 45 °C with 234 ml of ethyl formate, for 2 hours, and is subsequently cooled down to a temperature comprised between 20 and 25 °C for two additional hours. The resulting product is filtered and dried in a vacuum oven at a temperature of 30 °C, for four hours, to obtain 54 g of ethyl formate solvate of quinapril hydrochloride (Yield: 95%).

IR (KBr) (ν, cm^{-1}) : 3520, 3028, 3001, 2979, 2935, 2857, 1744, 1718, 1648, 1546, 1495, 1462, 1454, 1432, 1388, 1260, 1199, 756.

In solution, this compound is a mixture of two rotamers. The distribution of the rotamers is observed, in some cases, in the proton and carbon 13 nuclear magnetic resonance (NMR) spectra.

^{1}H-NMR ($CDCl_3$, 300 MHz) (δ(ppm)): 10,00 (s wide, 1H), 8,95 (s wide, 1H), 8,02 (s, 1H); 7,15 (m, 9H); 5,15 (J_1 = J_2 = 5,6 Hz), 4,95 ($width_{min}$), 1H; 4,82 - 4,62 (m, 2H); 4,60 - 4,42 (m, 1H); 4,20 (q, (J_1 = J_2 = J_3 = 7,0 Hz, 2H); 4,09 - 3,90 (m, 1H); 3,68 (q_{min}); 3,40 - 3,05 (m, 2H), 2,97 - 2,59 (m, 2H); 2,42 - 2,20 (m, 2H); 1,67 (d, J_1 = 7,0 Hz), 1,56 (d_{min}, J_1 = 7,0 Hz, 1H), 1,30 (t, J_1 = J_2 = 7,0 Hz), 1,18 (J_1 = J_2 = 7,0 Hz), 3H.

^{13}C-NMR ($CDCl_3$, 75 MHz) (δ(ppm)): 172,2, 171,3 (min), 169,2 (min), 168,6, 168,0, 161,0, 139,7 (min), 139,4,

132,2, 131,4 (min), 131,3 (min), 131,2, 128,5 (min), 128,4, 128,2, 127,2, 127,1, 126,3, 126,2, 126,1, 63,1 (min), 62,9, 59,9, 59,1 (min), 58,9, 58,2 (min), 54,8 (min), 54,6 (min), 54,5, 53,1, 45,4, 44,1 (min), 31,8 (min), 31,3, 31,1, 31,0, 30,8 (min), 30,1, 16,2 (min), 15,2, 14,1, 14,0 (min), 13,9.

X-Ray Diffraction (powder)

Ethyl formate solvate of quinapril hydrochloride

Angle (2θ°)	Relative intensity (%)
8,82	32,7
10,88	23,3
11,47	20,9
12,05	16,5
13,63	34,4
15,89	12,5
16,08	17,2
16,48	27,4
16,85	32,7
18,05	10,4
18,42	17,8
18,68	24,6
19,52	50,7
19,75	33,2
20,11	45,3
21,20	36,6
21,86	100,0
23,07	15,3
23,59	30,1
24,50	42,5
26,66	14,5
27,16	22,7
27,45	10,6
28,34	13,1

28,71	15,6
29,66	29,5
30,56	14,5
34,87	13,5

2.3. Methyl acetate solvate of quinapril hydrochloride

Following a similar process to that described in Example 2.2., but changing ethyl formate for methyl acetate, the corresponding methyl acetate solvate of quinapril hydrochloride (Yield: 95%) was obtained, which is characterised by the following spectroscopic data.

IR (KBr) (ν, cm^{-1}) : 3500, 3084, 3003, 2860, 1746, 1735, 1706, 1648, 1545, 1495, 1455, 1259, 1196, 755.

In solution, this compound is a mixture of two rotamers. The distribution of the rotamers is observed, in some cases, in the proton and carbon 13 nuclear magnetic resonance (NMR) spectra.

^{1}H-NMR ($CDCl_3$, 300 MHz) (δ(ppm)): 10,10 (s wide, 1H); 9,10 (s wide, 1H); 7,21 - 7,06 (m, 9H); 5,14 (t, $J_1 = J_2 =$ 5,6 Hz, 1H); 4,80 - 4,67 (m, 2H); 4,57 (m, 1H); 4,21 - 4,19 (m, 2H); 4,16 - 3,89 (m, 1H); 3,66 (s, 3H); 3,41 - 3,00 (m, 2H); 2,72 - 2,62 (m, 2H); 2,34 - 2,29 (m, 2H); 2,05 (s, 3H); 1,67 (d, J_1 = 6,8 Hz), 1,57 (d_{min}, J_1 = 6,8 Hz), 3H; 1,21 (t_{min} , $J_1 = J_2$ = 6,9 Hz); 1,17 (t, $J_1 = J_2$ = 6,9 Hz), 3H.

^{13}C-NMR ($CDCl_3$, 75 MHz) (δ(ppm)): 172,2, 171,5 (min), 169,2 (min), 168,6, 168,3 (min), 168,1, 139,6 (min), 139,4, 132,2, 131,5 (min), 131,3 (min), 131,2, 128,6, 128,5, 128,4, 128,3 (min), 127,8 (min), 127,2, 126,4, 126,2 (min), 63,2 (min), 62,9, 58,9, 54,7 (min), 54,5, 53,2, 51,5, 45,4, 44,2 (min), 31,9 (min), 31,4, 31,1, 31,0, 30,2 20,6, 16,1 (min), 15,5, 14,0 (min), 13,9.

X-Ray Diffraction (powder)

Methyl acetate solvate of quinapril hydrochloride

Angle (2θ°)	Relative intensity (%)
8,86	26,0
10,95	26,0
11,79	19,2
13,73	45,9
16,18	18,2
16,57	37,7
16,87	60,4
18,76	18,6
18,93	18,6
19,59	33,2
20,16	81,9
20,91	19,2
21,56	30,7
21,93	100,0
22,18	28,7
23,22	14,6
23,65	35,4
24,62	52,6
27,17	34,0
28,51	16,6
28,93	22,9
30,69	21,6
30,85	14,0

2.4. Quinapril hydrochloride

The ethyl formate or methyl acetate solvates of quinapril hydrochloride, obtained according to Examples 2.2. and 2.3., can be dried directly in a vacuum oven at a temperature comprised between 40 and 50 °C for a period of

time comprised between 12 and 14 hours, without the need of isolating them, in order to give the quinapril hydrochloride, which is a very scarcely crystalline or an amorphous product, as evidenced by its X-ray diffraction pattern. Out of the 54 g of ethyl formate solvate of quinapril hydrochloride 46 g of quinapril hydrochloride are obtained, characterised by:

- HPLC: 99.8%
- Titration: 100.2%
- $[\alpha]^R$ = +15.9° (2% methanol)

IR (KBr) (ν, cm^{-1}) : 3415, 3059, 2982, 2936, 1740, 1651, 1541, 1497, 1473, 1455, 1443, 1386, 1379, 1207, 751, 702.

In solution, quinapril hydrochloride is a mixture of two rotamers. The distribution of the rotamers is observed, in some cases, in the proton and carbon 13 nuclear magnetic resonance (NMR) spectra.

^{1}H-NMR ($CDCl_3$, 300 MHz) (δ(ppm)): 7,23, (m, 9H); 5,12 (m. 1H), 4,9 - 4,4 (m, 3H); 4,19 (m, 2H); 3,91 (m); 3,79 (m_{min}), 1H; 3,3 - 3,1 (m, 2H); 2,77 - 2,61 (m, 2H); 2,20 (m, 2H); 1,51 (d, J_1 = 6,4 Hz), 1,49 (d_{min}, J_1 = 5,1 Hz), 3H; 1,22 (t_{min}, $J_1 = J_2$ = 7,3 Hz), 1,17 (t, , $J_1 = J_2$ = 7,3 Hz), 3H.

^{13}C-NMR ($CDCl_3$, 75 MHz) (δ(ppm)): 171,5, 171,4, 168,5, 140,2, 132,5, 132,4, 132,1 (min), 131,5 (min), 128,5, 128,4, 128,2, 128,1, 127,1, 126,7, 126,6, 126,3, 126,1, 125,4, 62,2 (min), 62,0, 57,4 (min), 57,3, 53,9 (min), 53,1 (min), 52,7, 52,0, 44,5, 43,6 (min), 31,3 (min), 30,8, 30,6 (min), 30,4, 30,0, 21,1 (min), 16,2 (min), 14,7, 13,9.

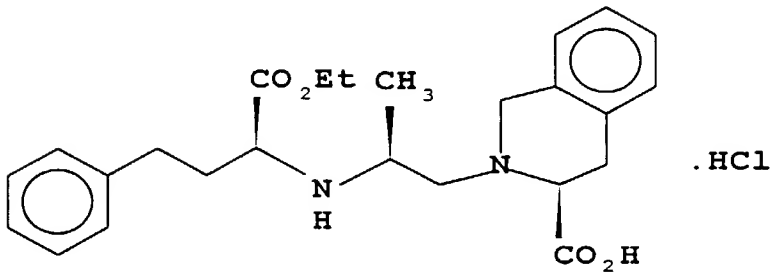
X-Ray Diffraction (powder)
Quinapril hydrochloride

Angle (2θ°)	Relative intensity (%)
11,18	31,9
12,17	29,4
17,38	33,9
19,83	37,9
28,34	10,0

Article 34

CLAIMS

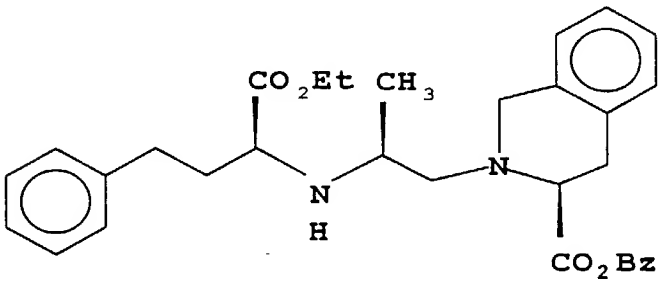
1. A process for obtaining quinapril hydrochloride of formula (I)



(I)

which comprises the stages of:

a) treatment of the benzyl ester of quinapril (II)



(II)

where Bz is the benzyl radical, with alcohol and hydrochloric acid or hydrogen chloride and hydrogenation of same through the addition of an appropriate hydrogenation catalyst;

b) removal of the solvent used in step a);

c) addition of toluene to precipitate the quinapril hydrochloride as a toluene solvate;

d) treatment of the toluene solvate of quinapril hydrochloride with a solvent belonging to class 3, capable of forming a solvate of quinapril hydrochloride from which it is possible to eliminate said solvent by drying in an oven without degrading the quinapril hydrochloride; and

e) drying of the solvate obtained in step d) at a temperature between 40°C and 50°C to yield quinapril hydrochloride (I)

2. A process according to claim 1 wherein the hydrogenolysis reaction of the benzyl ester of quinapril (II) is carried out in a alcoholic solvent, with treatment with concentrated hydrochloric acid or with a solution of hydrogen chloride in isopropanol, and hydrogenation with hydrogen gas in the presence of a hydrogenation catalyst.

3. A process according to claim 2, wherein said alcoholic solvent is chosen from between ethanol or isopropanol.

4. A process according to claim 2, wherein the hydrogenation is carried out at a pressure comprised 10^4 Pa and 2×10^5 Pa.

5. A process according to claim 2, wherein the hydrogenation is carried out at a temperature comprised 10 and 40°C.

6. A process according to claim 2, wherein the hydrogenation catalyst is Pd/C.

7. A process according to claim 2, wherein the hydrogenolysis reaction of the benzyl ester of quinapril (II) is carried out using ethanol as a solvent, concentrated hydrochloric acid, a pressure of 1×10^5 Pa (1 bar) and room temperature.

8. A process according to claim 2, wherein the hydrogenolysis reaction of the benzyl ester of quinapril (II) is carried out using isopropanol as a solvent, a

solution of hydrogen chloride in isopropanol, a pressure of 2 x 10^5 Pa (1 bar) and a temperature of approximately 30 °C.

9. A process according to claim 2 wherein the molar ratio between the benzyl ester of quinapril (II) and the hydrochloric acid can be equal or greater in a proportion of 1.1 (benzyl ester of quinapril (II)) to 1 (hydrochloric acid) with respect to stoichiometric one.

10. A process according to claim 1, wherein the removal of the solvent used in stage a) is carried out by vacuum-distillation.

11. A process according to claim 1, wherein the Class 3 solvent used to treat the toluene solvate of quinapril hydrochloride is chosen from among ethyl formate and methyl acetate.

12. A process according to claim 1, wherein the treatment of the toluene solvate of quinapril hydrochloride with the class 3 solvent is carried out at a temperature comprised between 40°C and 45°C, for a period of time comprised between 1 and 2 hours, and is subsequently cooled down to a temperatue comprised between 20 °C and 25 °C, for a period of time comprised between 1 and 2 hours.

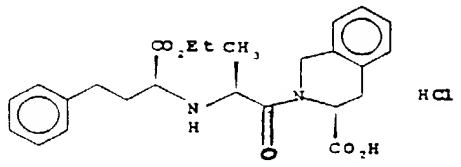
13. A process according to claim 1, wherein the Class 3 solvent solvate of quinapril hydrochloride is chosen from among ethyl formate solvate of quinapril hydrochloride and the methyl acetate solvate of quinapril hydrochloride.

14. A process according to claim 1, wherein the Class 3 solvent solvate of quinapril hydrochloride is dried in a vacuum oven , at a temperature comprised between 40 and 50 °C for a period of time comprised between 12 and 24 hours.

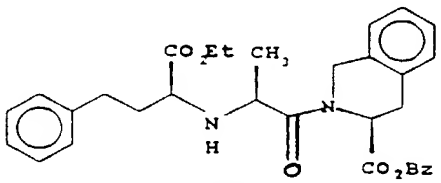
ABSTRACT

PROCESS FOR OBTAINING QUINAPRIL HYDROCHLORIDE AND SOLVATES USEFUL FOR THE ISOLATION AND PURIFICATION OF QUINAPRIL HYDROCHLORIDE

The process for obtaining quinapril hydrochloride (I) comprises the stages of: a) hydrogenolysis of the benzyl ester of quinapril (II) by treatment in an alcoholic solvent, with concentrated hydrochloric acid or a solution of hydrogen chloride in isopropanol, and hydrogenation; b) removal of the solvent; c) addition of toluene to precipitate the quinapril hydrochloride as a toluene solvate; d) treatment of said solvate with a Class 3 solvent which forms a solvate of quinapril hydrochloride from which it can be removed by drying without degrading; and e) drying of the solvate from step d) to yield quinapril hydrochloride (I), an antihypertensive agent.



(I)



(II)

Practitioner's Docket No. U 012500-4 ***PATENT***

COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL, CONTINUATION, OR C-I-P)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type:

(check one applicable item below)

[ ] original.
[ ] design.
[ ] supplemental.

NOTE: If the declaration is for an International Application being filed as a divisional, continuation or continuation-in-part application, do not check next item, check appropriate one of last three items.

[ ] national stage of PCT.

NOTE. If one of the following 3 items apply, then complete and also attach ADDED PAGES FOR DIVISIONAL, CONTINUATION OR C-I-P

NOTE. See 37 C F R. § 1.63(d) (continued prosecution application) for use of a prior nonprovisional application declaration in the continuation or divisional application being filed on behalf of the same or fewer of the inventors named in the prior application.

[ ] divisional.
[ ] continuation.

NOTE: Where an application discloses and claims subject matter not disclosed in the prior application, or a continuation or divisional application names an inventor not named in the prior application, a continuation-in-part application must be filed under 37 C.F.R. § 1 53(b) (application filing requirements-nonprovisional application).

[ ] continuation-in-part (C-I-P).

INVENTORSHIP IDENTIFICATION

WARNING: If the inventors are each not the inventors of all the claims, an explanation of the facts, including the ownership of all the claims at the time the last claimed invention was made, should be submitted.

My residence, post office address and citizenship are as stated below, next to my name. I believe that I am the original, first and sole inventor *(if only one name is listed below)* or an original, first and joint inventor *(if plural names are listed below)* of the subject matter that is claimed, and for which a patent is sought on the invention entitled:

TITLE OF INVENTION

PROCESS FOR OBTAINING QUINAPRIL HYDROCHLORIDE AND SOLVATES USEFUL FOR THE ISOLATION AND PURIFICATION OF QUINAPRIL HYDROCHLORIDE,

SPECIFICATION IDENTIFICATION

The specification of which:

(complete (a), (b), or (c))

(a) [ ] is attached hereto.

NOTE. "The following combinations of information supplied in an oath or declaration filed on the application filing date with a specification are acceptable as minimums for identifying a specification and compliance with any one of the items below will be accepted as complying with the identification requirement of 37 C F R. § 1.63:

"(1) name of inventor(s), and reference to an attached specification which is both attached to the oath or declaration at the time of execution and submitted with the oath or declaration on filing;

"(2) name of inventor(s), and attorney docket number which was on the specification as filed, or

"(3) name of inventor(s), and title which was on the specification as filed "

Notice of July 13, 1995 (1177 O G. 60).

(b) [ ] was filed on _____, [ ] as Application No. PCT/ES98/00145
[ ] and was amended on _____ *(if applicable).*

NOTE. Amendments filed after the original papers are deposited with the PTO that contain new matter are not accorded a filing date by being referred to in the declaration. Accordingly, the amendments involved are those filed with the application papers or, in the case of a supplemental declaration, are those amendments claiming matter not encompassed in the original statement of invention or claims. See 37 C F.R. § 1.67.

NOTE: "The following combinations of information supplied in an oath or declaration filed after the filing date are acceptable as minimums for identifying a specification and compliance with any one of the items below will be accepted as complying with the identification requirement of 37 C.F.R. § 1.63

"(1) name of inventor(s), and application number (consisting of the series code and the serial number; e.g.,08/123,456);

"(2) name of inventor(s), serial number and filing date;

"(3) name of inventor(s) and attorney docket number which was on the specification as filed;

"(4) name of inventor(s), title which was on the specification as filed and filing date;

"(5) name of inventor(s), title which was on the specification as filed and reference to an attached specification which is both attached to the oath or declaration at the time of execution and submitted with the oath or declaration; or

"(6) name of inventor(s), title which was on the specification as filed and accompanied by a cover letter accurately identifying the application for which it was intended by either the application number (consisting of the series code and the serial number; e.g.,08/123,456), or serial number and filing date. Absent any statement(s) to the contrary, it will be presumed that the application filed in the PTO is the application which the inventor(s) executed by signing the oath or declaration."

Notice of July 13, 1995 (1177 O.G. 60), M.P.E.P. § 601(a), 6th ed., rev.3.

(c) [ ] was described and claimed in PCT International Application No. _____ filed on _____ and as amended under PCT Article 19 on _____ *(if any)*.

SUPPLEMENTAL DECLARATION (37 C.F.R. § 1.67(b))

(complete the following where a supplemental declaration is being submitted)

[ ] I hereby declare that the subject matter of the

[ ] attached amendment
[ ] amendment filed on _____.

was part of my/our invention and was invented before the filing date of the original application, above identified, for such invention.

ACKNOWLEDGMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information, which is material to patentability as defined in 37, Code of Federal Regulations, § 1.56,

(also check the following items, if desired)

[ ] and which is material to the examination of this application, namely, information where there is a substantial likelihood that a reasonable Examiner would consider it important in deciding whether to allow the application to issue as a patent, and

[ ] in compliance with this duty, there is attached an information disclosure statement, in accordance with 37 C.F.R. § 1.98.

PRIORITY CLAIM (35 U.S.C. § 119(a)-(d))

NOTE: "The claim to priority need be in no special form and may be made by the attorney or agent if the foreign application is referred to in the oath or declaration as required by § 1.63. The claim for priority and the certified copy of the foreign application specified in 35 U.S.C. § 119(b) must be filed in the case of an interference (§ 1.630), when necessary to overcome the date of a reference relied upon by the examiner, when specifically required by the examiner, and in all other situations, before the patent is granted If the claim for priority or the certified copy of the foreign application is filed after the date the issue fee is paid, it must be accompanied by a petition requesting entry and by the fee set forth in § 1.17(i) If the certified copy is not in the English language, a translation need not be filed except in the case of interference; or when necessary to overcome the date of a reference relied upon by the examiner; or when specifically required by the examiner, in which event an English language translation must be filed together with a statement that the translation of the certified copy is accurate." 37 C.F.R. § 1.55(a).

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

(complete (d) or (e))

(d) [ ] no such applications have been filed.
(e) [ ] such applications have been filed as follows.

NOTE: Where item (c) is entered above and the International Application which designated the U.S itself claimed priority check item (e), enter the details below and make the priority claim.

PRIOR FOREIGN/PCT APPLICATION(S) FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS APPLICATION AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. § 119(a)-(d)

COUNTRY (OR INDICATE IF PCT)	APPLICATION NUMBER	DATE OF FILING DAY, MONTH, YEAR	PRIORITY CLAIMED UNDER 35 USC 119
SPAIN	P 9701169	29 May 1997	[x] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO

CLAIM FOR BENEFIT OF PRIOR U.S. PROVISIONAL APPLICATION(S)
(35 U.S.C. § 119(e))

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below:

PROVISIONAL APPLICATION NUMBER	FILING DATE
_____ / _____	_____
_____ / _____	_____
_____ / _____	_____

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S) UNDER 35 U.S.C. § 120

[ ] The claim for the benefit of any such applications are set forth in the attached ADDED PAGES TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR DIVISIONAL, CONTINUATION OR CONTINUATION-IN-PART (C-I-P) APPLICATION.

ALL FOREIGN APPLICATION(S), *IF ANY,* FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

_____

_____

_____

NOTE: If the application filed more than 12 months from the filing date of this application is a PCT filing forming the basis for this application entering the United States as (1) the national stage, or (2) a continuation, divisional, or continuation-in-part, then also complete ADDED PAGES TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR DIVISIONAL, CONTINUATION OR C-I-P APPLICATION for benefit of the prior U.S or PCT application(s) under 35 U.S.C. § 120

POWER OF ATTORNEY

I hereby appoint the following practitioner(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

(list name and registration number)

JOSEPH H. HANDELMAN, 26179
JOHN RICHARDS, 31053
RICHARD J. STREIT, 25765
PETER D. GALLOWAY, 27885
IAN C. BAILLIE, 24090
THOMAS F. PETERSON, 24790
RICHARD P. BERG, 28145
JULIAN H. COHEN, 20302
WILLIAM R. EVANS, 25858
JANET I. CORD, 33778
CLIFFORD J. MASS, 30086
CYNTHIA R. MILLER, 34678

(Check the following item, if applicable)

[ ] I hereby appoint the practitioner(s) associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

[ ] Attached, as part of this declaration and power of attorney, is the authorization of the above-named practitioner(s) to accept and follow instructions from my representative(s).

SEND CORRESPONDENCE TO

DIRECT TELEPHONE CALLS TO:
(Name and telephone number)

Ladas & Parry
26 West 61st Street
New York, N.Y. 10023

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

NOTE: Carefully indicate the family (or last) name, as it should appear on the filing receipt and all other document.

NOTE: Each inventor must be identified by full name, including the family name, and at least one given name without abbreviation together with any other given name or initial, and by his/her residence, post office address and country of citizenship. 37 C.F.R § 1.63(a)(3)

NOTE: Inventors may execute separate declarations/oaths provided each declaration/oath sets forth all the inventors. Section 1 63(a)(3) requires that a declaration/oath, inter alia, identify each inventor and prohibits the execution of separate declarations/oaths which each sets forth only the name of the executing inventor 62 Fed. Reg 53,131, 53,142, October 10, 1997.

Full name of sole or first inventor

1-00

MONTSERRAT (*Given Name*) _____ (*Middle Initial or Name*) MONSALVATJE LLAGOSTERA (*Family (Or Last Name)*)

Inventor's signature (X) MONSALVATJE LLAGOSTERA, Montserrat

Date (X) 13-04-00 **Country of Citizenship** SPAIN

Residence BARCELONA - SPAIN ESX

Post Office Address BARCELONA (SPAIN), Avenida Mare de Deu de Montserrat 12, 08024 Barcelona, Spain

---

Full name of second joint inventor, if any

2-00

MARTI (*Given Name*) _____ (*Middle Initial or Name*) BARTRA SANMARTI (*Family (Or Last Name)*)

Inventor's signature BARTRA SANMARTI, Martí

Date 13-04-00 **Country of Citizenship** SPAIN

Residence BARCELONA - SPAIN ESX

Post Office Address BARCELONA (SPAIN), Avenida Mare de Deu de Montserrat 12, 08024 Barcelona, Spain

---

Full name of third joint inventor, if any

3-00

JAIME (*Given Name*) _____ (*Middle Initial or Name*) TOMAS NAVARRO (*Family (Or Last Name)*)

Inventor's signature TOMAS NAVARRO, JAIME

Date 13-04-00 **Country of Citizenship** SPAIN

Residence BARCELONA - SPAIN ESX

Post Office Address BARCELONA (SPAIN), Avenida Mare de Deu de Montserrat 12, 08024 Barcelona, Spain

Practitioner's Docket No. U 012500-4

ADDED PAGE TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR SIGNATURE BY FOURTH AND SUBSEQUENT INVENTORS

Full name of fourth joint inventor, if any

Salvador _____ PUIG TORRES

(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature _____

Date _____ **Country of Citizenship** SPAIN

Residence BARCELONA - SPAIN

Post Office Address BARCELONA (SPAIN), Avenida Mare de Deu de Montserrat 12, 08024 Barcelona, Spain

---

Full name of fifth joint inventor, if any

_____ _____ _____

(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature _____

Date _____ **Country of Citizenship** _____

Residence _____

Post Office Address _____

Full name of sixth joint inventor, if any

_____ _____ _____

(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature _____

Date _____ **Country of Citizenship** _____

Residence _____

Post Office Address _____

(check proper box(es) for any of the following added page(s) that form a part of this declaration)

[ ] **Signature** for fourth and subsequent joint inventors. *Number of pages added* _____

* * *

[ ] **Signature** by administrator(trix), executor(trix) or legal representative for deceased or incapacitated inventor. *Number of pages added* _____

* * *

[ ] **Signature** for inventor who refuses to sign or cannot be reached by person authorized under 37 C.F.R. § 1.47. *Number of pages added* _____

* * *

[ ] Added page for **signature** by one joint inventor on behalf of deceased inventor(s) where legal representative cannot be appointed in time. (37 C.F.R. § 1.47)

* * *

[ ] Added pages to combined declaration and power of attorney for divisional, continuation, or continuation-in-part (C-I-P) application.

[ ] Number of pages added _____

* * *

[ ] Authorization of practitioner(s) to accept and follow instructions from representative.

(If no further pages form a part of this Declaration, then end this Declaration with this page and check the following item)

[X] This declaration ends with this page.

Practitioner's Docket No. U 012500-4 *PATENT*

COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL, CONTINUATION, OR C-I-P)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type:

(check one applicable item below)

☐ original.

☐ design.

NOTE: With the exception of a supplemental oath or declaration submitted in a reissue, a supplemental oath or declaration is not treated as an amendment under 37 CFR 1 312 (Amendments after allowance). M P.E P Section 714 16, 7th Ed.

☐ supplemental.

NOTE: If the declaration is for an International Application being filed as a divisional, continuation or continuation-in-part application, do not check next item; check appropriate one of last three items

☒ national stage of PCT.

NOTE: If one of the following 3 items apply, then complete and also attach ADDED PAGES FOR DIVISIONAL, CONTINUATION OR C-I-P.

NOTE See 37 C F R Section i 63(d) (continued prosecution application) for use of a prior nonprovisional application declaration in the continuation or divisional application being filed on behalf of the same or fewer of the inventors named in the prior application.

☐ divisional.

☐ continuation.

NOTE: Where an application discloses and claims subject matter not disclosed in the prior application, or a continuation or divisional application names an inventor not named in the prior application, a continuation-in-part application must be filed under 37 C F R Section 1 53(b) (application filing requirements-nonprovisional application).

☐ continuation-in-part (C-I-P).

INVENTORSHIP IDENTIFICATION

WARNING: If the inventors are each not the inventors of all the claims, an explanation of the facts, including the ownership of all the claims at the time the last claimed invention was made, should be submitted.

My residence, post office address and citizenship are as stated below, next to my name. I believe that I

am the original, first and sole inventor *(if only one name is listed below)* or an original, first and joint inventor *(if plural names are listed below)* of the subject matter that is claimed, and for which a patent is sought on the invention entitled:

TITLE OF INVENTION

PROCESS FOR OBTAINING QUINAPRIL HYDROCHLORIDE AND SOLVATES USEFUL FOR THE ISOLATION AND PURIFICATION OF QUINAPRIL HYUDROCHLORIDE

SPECIFICATION IDENTIFICATION

The specification of which:

(complete (a), (b), or (c))

(a) ☐ is attached hereto.

NOTE. "The following combinations of information supplied in an oath or declaration filed on the application filing date with a specification are acceptable as minimums for identifying a specification and compliance with any one of the items below will be accepted as complying with the identification requirement of 37 C.F.R. Section 1.63:

"(1) name of inventor(s), and reference to an attached specification which is both attached to the oath or declaration at the time of execution and submitted with the oath or declaration on filing;

"(2) name of inventor(s), and attorney docket number which was on the specification as filed; or

"(3) name of inventor(s), and title which was on the specification as filed."

Notice of July 13, 1995 (1177 O.G. 60).

(b) ☒ was filed on 29/11/99, ☐ as Application No. 09/424,673

☐ and was amended on _____ (if applicable).

NOTE. Amendments filed after the original papers are deposited with the PTO that contain new matter are not accorded a filing date by being referred to in the declaration. Accordingly, the amendments involved are those filed with the application papers or, in the case of a supplemental declaration, are those amendments claiming matter not encompassed in the original statement of invention or claims. See 37 C.F.R. Section 1.67.

NOTE "The following combinations of information supplied in an oath or declaration filed after the filing date are acceptable as minimums for identifying a specification and compliance with any one of the items below will be accepted as complying with the identification requirement of 37 C.F.R Section 1.63:

(A) application number (consisting of the series code and the serial number, e.g., 08/123,456);

(B) serial number and filing date;

(C) attorney docket number which was on the specification as filed;

(D) title which was on the specification as filed and reference to an attached specification which is both attached to the oath or declaration at the time of execution and submitted with the oath or declaration; or

(E) title which was on the specification as filed and accompanied by a cover letter accurately identifying the application for which it was intended by either the application number (consisting of the series code and the serial number, e.g., 08/123,456), or serial number and filing date. Absent any statement(s) to the contrary, it will be presumed that the application filed in the PTO is the application which the inventor(s) executed by signing the oath or declaration.

M.P.E.P. Section 601.01(a), 7th ed.

(c) ☒ was described and claimed in PCT International Application No. PCT/ES98/00145 filed on May 25, 1998 and as amended under PCT Article 19 on _____ *(if any)*.

SUPPLEMENTAL DECLARATION (37 C.F.R. Section 1.67(b))

(complete the following where a supplemental declaration is being submitted)

☐ I hereby declare that the subject matter of the

☐ attached amendment

☐ amendment filed on _____.

was part of my/our invention and was invented before the filing date of the original application, above identified, for such invention.

ACKNOWLEDGMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information, which is material to patentability as defined in 37, Code of Federal Regulations, Section 1.56.

(also check the following items, if desired)

☐ and which is material to the examination of this application, namely, information where there is a substantial likelihood that a reasonable Examiner would consider it important in deciding whether to allow the application to issue as a patent, and

☐ in compliance with this duty, there is attached an information disclosure statement, in accordance with 37 C.F.R. Section 1.98.

PRIORITY CLAIM (35 U.S.C. Section 119(a)-(d))

NOTE. "The claim to priority need be in no special form and may be made by the attorney or agent if the foreign application is referred to in the oath or declaration as required by Section 1 63 The claim for priority and the certified copy of the foreign application specified in 35 U S C Section 119(b) must be filed in the case of an interference (Section 1 630), when necessary to overcome the date of a reference relied upon by the examiner, when specifically required by the examiner, and in all other situations, before the patent is granted. If the claim for priority or the certified copy of the foreign application is filed after the date the issue fee is paid, it must be accompanied by a petition requesting entry and by the fee set forth in Section 1 17(i) If the certified copy is not in the English language, a translation need not be filed except in the case of interference; or when necessary to overcome the date of a reference relied upon by the examiner; or when specifically required by the examiner, in which event an English language translation must be filed together with a statement that the translation of the certified copy is accurate." 37 C F R Section 1.55(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

(complete (d) or (e))

(d) ☐ no such applications have been filed.

(e) ☒ such applications have been filed as follows.

NOTE: Where item (c) is entered above and the International Application which designated the U S. itself claimed priority check item (e), enter the details below and make the priority claim.

PRIOR FOREIGN/PCT APPLICATION(S) FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS APPLICATION AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. SECTION 119(a)-(d)

COUNTRY (OR INDICATE IF PCT)	APPLICATION NUMBER	DATE OF FILING DAY, MONTH, YEAR	PRIORITY CLAIMED UNDER 35 USC 119
SPAIN	P 9701169	29 May 1997	☒YES ☐NO
			☐YES ☐NO
			☐YES ☐NO
			☐YES ☐NO
			☐YES ☐NO

CLAIM FOR BENEFIT OF PRIOR U.S. PROVISIONAL APPLICATION(S)
(35 U.S.C. Section 119(e))

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below:

PROVISIONAL APPLICATION NUMBER	FILING DATE
_____ / _____	_____
_____ / _____	_____
_____ / _____	_____

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S) UNDER 35 U.S.C. SECTION 120

☐ The claim for the benefit of any such applications are set forth in the attached ADDED PAGES TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR DIVISIONAL, CONTINUATION OR CONTINUATION-IN-PART (C-I-P) APPLICATION.

ALL FOREIGN APPLICATION(S), *IF ANY*, FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

_____

_____

_____

NOTE: If the application filed more than 12 months from the filing date of this application is a PCT filing forming the basis for this application entering the United States as (1) the national stage, or (2) a continuation, divisional, or continuation-in-part then also complete ADDED PAGES TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR DIVISIONAL, CONTINUATION OR C-I-P APPLICATION for benefit of the prior U.S. or PCT application(s) under 35 U.S.C. Section 120

POWER OF ATTORNEY

I hereby appoint the following practitioner(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

(list name and registration number)

JOSEPH H. HANDELMAN, 26179	RICHARD P. BERG, 28145
JOHN RICHARDS, 31053	JULIAN H. COHEN, 20302
RICHARD J. STREIT, 25765	WILLIAM R. EVANS 25858
PETER D. GALLOWAY, 27885	JANET I. CORD, 33778
IAN C. BAILLIE, 24090	CLIFFORD J. MASS, 30086
THOMAS F. PETERSON, 24790	CYNTHIA R. MILLER, 34678

(Check the following item, if applicable)

☐ I hereby appoint the practitioner(s) associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

☐ Attached, as part of this declaration and power of attorney, is the authorization of the above-named practitioner(s) to accept and follow instructions from my representative(s).

NOTE. "Special care should be taken in continuation or divisional applications to ensure that any change of correspondence address in a prior application is reflected in the continuation or divisional application. For example, where a copy of the oath or declaration from the prior application is submitted for a continuation or divisional application filed under 37 CFR 1.53(b) and the copy of the oath or declaration from the prior application designates an old correspondence address, the Office may not recognize, in the continuation or divisional application, the change of correspondence address made during the prosecution of the prior application. Applicant is required to identify the change of correspondence address in the continuation or divisional application to ensure that communications from the Office are mailed to the current correspondence address. 37 CFR 1.63(d)(4)." Section 601.03, M.P.E.P., 7th Ed.

SEND CORRESPONDENCE TO

Ladas & Parry
26 West 61st Street
New York, N.Y. 10023

DIRECT TELEPHONE CALLS TO:
(Name and telephone number)

(212) 708-1930

(complete the following if applicable)

Since this filing is a [ ] continuation [ ] divisional there is attached hereto a Change of Correspondence Address so that there will be no question as to where the PTO should direct all correspondence.

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

NOTE *Carefully indicate the family (or last) name, as it should appear on the filing receipt and all other document*

NOTE. *Each inventor must be identified by full name, including the family name, and at least one given name without abbreviation together with any other given name or initial, and by his/her residence, post office address and country of citizenship. 37 C.F.R § 1.63(a)(3)*

NOTE *Inventors may execute separate declarations/oaths provided each declaration/oath sets forth all the inventors Section 1 63(a)(3) requires that a declaration/oath, inter alia, identify each inventor and prohibits the execution of separate declarations/oaths which each sets forth only the name of the executing inventor 62 Fed Reg 53,131, 53,142, October 10, 1997.*

Full name of sole or first inventor

Montserrat _____ _____ MONSALVATJE LLAGOSTERA

(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature (X) _____

Date (X)_____ **Country of Citizenship** Spain

Residence Barcelona, Spain

Post Office Address Avenida Mare de Deu de Montserrat, 12
08024 Barcelona, Spain

Full name of second joint inventor, if any

Marti _____ _____ BARTRA SANMARTI

(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature _____

Date _____ **Country of Citizenship** Spain

Residence Barcelona, Spain

Post Office Address Avenida Mare de Deu de Montserrat, 12
08024 Barcelona, Spain

Full name of third joint inventor, if any

Jaime _____ _____ TOMAS NAVARRO

(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature _____

Date _____ **Country of Citizenship** Spain

Residence Barcelona, Spain

Post Office Address Avenida Mare de Deu de Montserrat, 12
08024 Barcelona, Spain

(check proper box(es) for any of the following added page(s) that form a part of this declaration)

[X] **Signature** for fourth and subsequent joint inventors. *Number of pages added* 1

* * *

[ ] **Signature** by administrator(trix), executor(trix) or legal representative for deceased or incapacitated inventor. *Number of pages added* _____

* * *

[ ] **Signature** for inventor who refuses to sign or cannot be reached by person authorized under 37 C.F.R. § 1.47. *Number of pages added* _____

* * *

[ ] Added page for **signature** by one joint inventor on behalf of deceased inventor(s) where legal representative cannot be appointed in time. (37 C.F.R. § 1.47)

* * *

[ ] Added pages to combined declaration and power of attorney for divisional, continuation, or continuation-in-part (C-I-P) application.

[ ] Number of pages added _____

* * *

[ ] Authorization of practitioner(s) to accept and follow instructions from representative.

(If no further pages form a part of this Declaration, then end this Declaration with this page and check the following item)

[ ] This declaration ends with this page.

Practitioner's Docket No. U 012500-4

4-w

ADDED PAGE TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR SIGNATURE BY FOURTH AND SUBSEQUENT INVENTORS

Full name of fourth joint inventor, if any

Salvador | | PUIG TORRES

(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature Salvador Puig

Date 4/6/2002 **Country of Citizenship** Spain

Residence Barcelona, Spain ESX

Post Office Address Av. Icària, 149, 2on 1ª

08005 BARCELONA - SPAIN

Full name of fifth joint inventor, if any

(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature _____

Date _____ **Country of Citizenship** _____

Residence _____

Post Office Address _____

Full name of sixth joint inventor, if any

(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature _____

Date _____ **Country of Citizenship** _____

Residence _____

Post Office Address _____